

Nivolumab-Induced Rapid Tumor Remission of Pulmonary Adenocarcinoma

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Abstract

We The immune checkpoint modulator, nivolumab (BMS-936558/ONO-4538), is the first PD-1 inhibitor to gain regulatory approval, for the treatment of patients with unresectable melanoma. Nivolumab received FDA approval for the treatment of melanoma in December 2014. On 24 April 2015, the Committee for Medical Products for Human Use of the European Medicine Agency recommended approval of Nivolumab for metastatic melanoma as a monotherapy. In March 2015, the US FDA approved it for the treatment of squamous non-small cell lung cancer.

This case reports about a patient with metastatical pulmonary adenocarcinoma who benefited from the therapy with nivolumab. Already after 10 weeks of treatment with nivolumab, we registered rapid tumor remission.

Keywords: Non-small cell lung cancer; Programmed death-1; Programmed death-1 ligand; Epidermal growth factor receptor; Anaplastic lymphoma kinase; Proto-oncogene tyrosine-protein kinase ROS; Antibody-dependent cellular cytotoxicity; Immune-related progression-free survival; Human immunoglobulin G4

Case Report

The A 43-year-old nonsmoking woman was referred to our center due to increased dyspnea and hemoptysis. She was in reduced functional status (ECOG I). Contrast-enhanced-CT-scan revealed a tumor mass in the left lower lobe (Figure 1a). Histology revealed a non-small cell lung

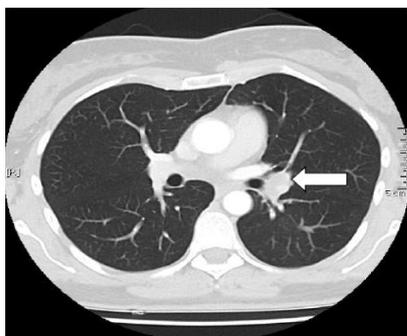


Figure 1a: CT- scan revealed a tumor mass in the left lower lobe before the chemotherapy with carboplatin and vinorelbine.

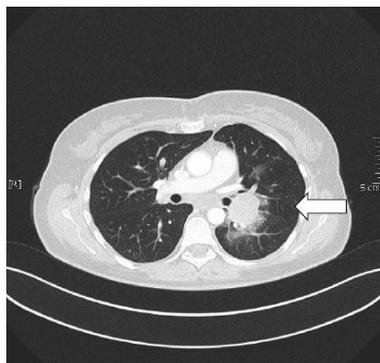


Figure 1b: Reevaluation showed tumor progression after 2 cycles of carboplatin and vinorelbine.



Figure 2a: CT-Scan showed huge tumor mass after 2 cycles of carboplatin and vinorelbine.

carcinoma, pulmonary adenocarcinoma, and further immunological evaluation revealed no mutations of EGFR or rearrangements of the anaplastic lymphoma kinase ALK.

The staging- procedure revealed osseous and cerebral metastasis. Therefore, a combined therapy consisting of palliative chemotherapy with carboplatin and vinorelbine, palliative radiation of osseous and cerebral metastasis was also initiated. Due to reduced renal function, pemetrexed was not feasible.

After 2 cycles of carboplatin and vinorelbine, thoracic CT-scan revealed tumor progression (Figure 1b).

We initiated second- line therapy with nivolumab. The weight related dosage of nivolumab was between 180 mg and 190 mg. Within 10 weeks after 5 cycles of nivolumab, the reevaluation revealed significant pulmonary tumor remission (Figure 2a and 2b).

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After significant tumor remission, an immunological treatment with further 6 cycles of nivolumab was accomplished. CT-scan revealed stable disease under maintenance treatment (Figure 3a and 3b). The

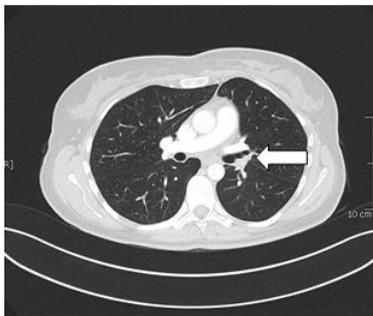


Figure 2b: CT-Scan revealed significant tumor remission after 5 cycles of nivolumab.



Figure 3a: CT-Scan revealed tumor remission after 5 cycles of nivolumab.



Figure 3b: CT-Scan revealed stable disease, with no signs of progression after 6 cycles of maintenance therapy.

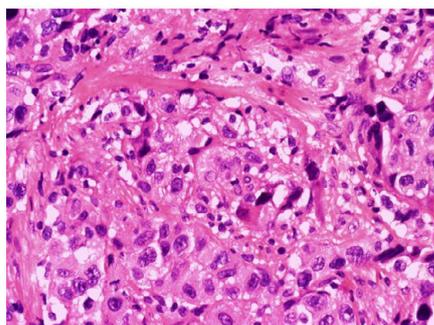


Figure 4: H&E staining of biopsy specimens shows small clusters of non-small cell carcinoma without any glandular differentiation (x400).

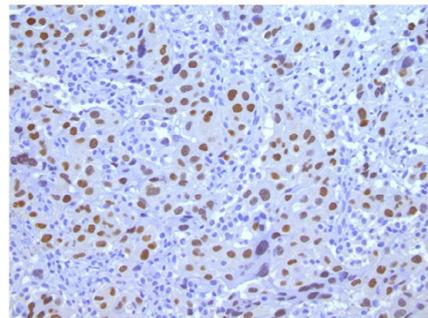


Figure 5: Nuclear staining of tumor cells for TTF1 favors the diagnosis of pulmonary adenocarcinoma (x200).

clinical conditioning of the patient also improved through the therapy with nivolumab.

Histology

Histological examination revealed a poorly differentiated non-small cell carcinoma without clear glandular differentiation by routine light microscopy (Figure 4). Nuclear expression of TTF1 in tumor cells strongly supported the diagnosis of pulmonary adenocarcinoma (Figure 5).

After 10 cycles of nivolumab, we were also able to achieve slightly cerebral remission and osseous stable disease.

There will be reevaluation after every 5 cycles of the treatment with nivolumab. The patient tolerated the therapy very well, with no serious adverse events such as dyspnea, pneumonitis and diarrhea.

Discussion

Nivolumab is a genetically engineered, fully human immunoglobulinG4 (IgG4) monoclonal antibody specific for human PD-1. The IgG4 isotype was engineered to obviate antibody-dependent cellular cytotoxicity (ADCC). Most monoclonal antibodies in therapeutic oncology contain the IgG1 subtype, which have the most significant ADCC whereas IgG4 subtype possesses minimal ADCC activity. An intact ADCC has the potential to deplete activated T cells and tumor-infiltrating lymphocytes and diminish activity as PD-1 is expressed on T effector cells and other immune cells [1]. Nivolumab binds PD-1 with high affinity (KD 2.6 nmol/l by Scatchard analysis to polyclonal activated human T cells) and blocks its interactions with both B7-H1 and B7-DC [2].

We report a young female non-smoking patient with first diagnosis of pulmonary adenocarcinoma with osseous and cerebral metastasis. Histological analysis showed no EGFR-mutation or ALK-translocations. The CT-scan revealed severe tumor progression after 2 cycles of carboplatin and vinorelbine. We initiated the second line therapy with nivolumab.

The study of Brahmer et al. showed that nivolumab has a longer median overall survival compared with docetaxel [3]. Also, the study showed that nivolumab has significant higher overall survival rate, higher response rate and longer median progression-free survival compared with docetaxel [3]. The frequencies of both hematologic and non-hematologic adverse events, including severe toxic events were substantially less with nivolumab than with docetaxel [3].

As the frequency of PDL-1 positive NSCLC tumors is about 20% [4], potentially a large number of patients with advanced stage NSCLC may

be suitable for nivolumab treatment. In comparison, the frequency of patients with EML-ALK translocation or ROS1 rearrangement is about 4% [5] and 1% to 2% [6] respectively, depending on the population studied and detection methods used.

Pneumonitis is a serious adverse event and is of major concern in lung cancer patients who may already have poor lung reserve due to prior smoking or metastatic disease. Pneumonitis rates for nivolumab are similar to or lower than rates of other commonly used drugs in NSCLC such as docetaxel (4.6%) [7] and gefitinib (3.5%) [8].

Our patient tolerated the medication very well. Pneumonitis, rash and diarrhea were not registered. We have monitored our patient closely, during the therapy interval (every 2 weeks).

One of the challenges faced in the development of nivolumab and other inhibitors of the PD-1/PDL-1 pathway is the assessment of tumor response. The use of RECIST 1.1 for tumor assessment in patients receiving immunotherapy has limitations. For example, RECIST 1.1 is not suitable for patients who initially progress as defined by RECIST 1.1 but subsequently respond or (ii) patients with a mixed response or new lesions, but the overall tumor burden is decreased. Based on this, an immune-related response criterion has been proposed [9]. Immune-related progression-free survival (irPFS) accounts for the apparent increase in tumor size followed by sustained tumor response, which has been documented with these agents in the past [10]. This phenomenon of 'pseudo-progression' may be due to peritumoral lymphocyte infiltration or delayed immune activity [10].

In our case, CT-scan after 5 cycle of nivolumab revealed impressive rapid tumor remission according to RECIST criteria. The patient strongly benefited from the therapy with nivolumab, also tolerated the therapy very well. At present, nivolumab is a new standard second line therapeutic option in NSCLC regardless of histological subtype.

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